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ORIGINAL RESEARCH

Microvolt QRS Alternans Without Microvolt T-Wave Alternans in Human Cardiomyopathy: A Novel Risk Marker of Late Ventricular Arrhythmias

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BACKGROUND: Action potential alternans can induce ventricular tachyarrhythmias and manifest on the surface ECG as T-wave alternans (TWA) and QRS alternans (QRSA). We sought to evaluate microvolt QRSA in cardiomyopathy patients in relation to TWA and ventricular tachyarrhythmia outcomes.

METHODS AND RESULTS: Prospectively enrolled cardiomyopathy patients (n=100) with prophylactic defibrillators had 12-lead ECGs recorded during ventricular pacing from 100 to 120 beats/min. QRSA and TWA were quantified in moving 128-beat segments using the spectral method. Segments were categorized as QRSA positive (QRSA+) and/or TWA positive (TWA+) based on ≥2 precordial leads having alternans magnitude >0 and signal:noise >3. Patients were similarly categorized based on having ≥3 consecutive segments with alternans. TWA+ and QRSA+ occurred together in 31% of patients and alone in 18% and 14% of patients, respectively. Although TWA magnitude (1.4±0.4 versus 4.7±1.0 μV, $P<0.01$) and proportion of TWA+ studies (16% versus 46%, $P<0.01$) increased with rate, QRSA did not change. QRS duration was longer in QRSA+ than QRSA-negative patients (138±23 versus 113±26 ms, $P<0.01$). At 3.5 years follow-up, appropriate defibrillator therapy or sustained ventricular tachyarrhythmia was greater in QRSA+ than QRSA-negative patients (30% versus 8%, $P=0.02$) but similar in TWA+ and TWA-negative patients. Among QRSA+ patients, the event rate was greater in those without TWA (62% versus 21%, $P=0.02$). Multivariable Cox analysis revealed QRSA+ (hazard ratio [HR], 4.6; 95% CI, 1.5–14; $P=0.009$) and QRS duration >120 ms (HR, 4.1; 95% CI, 1.3–12; $P=0.014$) to predict events.

CONCLUSIONS: Microvolt QRSA is novel phenomenon in cardiomyopathy patients that can exist without TWA and is associated with QRS prolongation. QRSA increases the risk of ventricular tachyarrhythmia 4-fold, which merits further study as a risk stratifier.

Key Words: cardiomyopathy ■ ECG ■ QRS alternans ■ T-wave alternans ■ ventricular arrhythmia

Action potential alternans describes the beat-to-beat changes in action potential shape and duration, which can be the harbinger of reentrant ventricular tachyarrhythmias (VA) as a result of increased repolarization gradients and functional conduction block.[1] Action potential alternans is dependent on heart rate and typically occurs at rapid rates from abnormal intracellular calcium cycling and oscillations in calcium-sensitive sarcolemma repolarizing currents.[2,3] During rapid pacing in ex vivo guinea pig hearts, epicardial optical action potential alternans, particularly during phase 2 and 3, gives rise to visible T-wave alternans (TWA) on a volume conductor ECG recording.[1] In humans, lower magnitude TWA has also been

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CLINICAL PERSPECTIVE

What Is New?

- Microvolt QRS alternans induced with rapid ventricular pacing is a novel phenomenon in cardiomyopathy patients and can exist with (in 31% of patients) or without (in 14%) microvolt T-wave alternans.
- Microvolt QRS alternans is associated with QRS prolongation, suggesting His-Purkinje and/or myocardial conduction alternans as a putative mechanism.
- Microvolt QRS alternans independently increases the risk of late ventricular arrhythmias 4-fold, with the greatest event rates being observed in patients without concurrent microvolt T-wave alternans.

What Are the Clinical Implications?

- The vast majority of cardiomyopathy patients receiving prophylactic defibrillators, based on current practice guidelines, do not receive appropriate therapy and are at risk of implant-related complications.
- Microvolt QRS alternans is a strong ECG-based risk stratifier that may improve patient selection for prophylactic defibrillator therapy, although this will require validation in a larger multicenter prospective study.
- Future mapping studies should investigate the pathogenesis of microvolt QRS alternans and its relation to ventricular arrhythmias.

Nonstandard Abbreviations and Acronyms

bpm	beats per minute
HPM	His-Purkinje and/or myocardial
HR	hazard ratio
ICD	implantable cardioverter defibrillator
QRSA	QRS alternans
S_{NB}	alternans mean noise
SVT	supraventricular tachycardia
TWA	T-wave alternans
VA	ventricular tachyarrhythmia
V_{alt}	alternans magnitude
VT	ventricular tachycardia

detected from intracardiac electrogram recordings and body surface electrocardiography, typically in the microvolt range.[4–7] Temporal surges in the magnitude of microvolt TWA have been detected from implantable cardioverter defibrillator (ICD) and Holter recordings before VA events in patients with cardiomyopathy,[6,8] further supporting the arrhythmogenic potential of microvolt-level TWA.

In ex vivo guinea pig hearts, action potential alternans can also give rise to visible QRS alternans (QRSA) but only during very rapid heart rates when action potential alternans involves phases 1 to 3.[1] In this experimental preparation, QRSA is always linked to TWA, but the heart rate onset for QRSA is faster than that for TWA. To date, visible QRSA has been reported only in patients with structurally normal hearts during rapid supraventricular tachycardia (SVT).[9,10] Although the mechanism is not well studied, visible QRSA in these patients is believed to arise from heart rate–dependent alternation in His-Purkinje conduction rather than abnormal intracellular calcium cycling.[10,11] In contrast to visible QRSA, microvolt-level QRSA has not been well described, nor is it understood how this phenomenon relates to microvolt TWA and the risk of VA in humans.

Our objective was to characterize microvolt QRSA in patients with cardiomyopathy and to describe its relationship to microvolt TWA. We also sought to determine whether microvolt QRSA would predict late-occurring VA independent of TWA.

METHODS

The authors declare that all supporting data are available within the article and its online supplementary files.

Patient Population

Patients with ischemic or nonischemic cardiomyopathy undergoing prophylactic ICD implantation according to current practice guidelines were prospectively enrolled from the University of Toronto teaching hospitals. Patients with prior VA or aborted cardiac arrest were excluded. All patients received guideline-based optimal heart failure medical therapy. In addition, a control group with left ventricular (LV) ejection fraction >50% and no documented VA, who underwent clinical electrophysiology study to evaluate VA risk but did not receive an ICD, were prospectively enrolled. The study was approved by the research ethics board at University Health Network, St. Michael's Hospital, and Sunnybrook Health Sciences Center, and all patients provided written informed consent.

Pacing Protocol and Alternans Analysis

Microvolt QRSA and TWA evaluation was performed at ICD clinic follow-up 1 to 6 months after ICD implantation in cardiomyopathy patients and during electrophysiology study in control patients. Ventricular pacing was performed consecutively at 100, 110, and 120 beats/min (bpm) for 3 minutes at each rate using the right ventricular ICD lead at follow-up or

a right ventricular quadripolar pacing catheter (Avail; Biosense Webster) at the time of electrophysiology study. Throughout pacing, digital 12-lead ECGs were continuously recorded at a sampling rate of 1 kHz using a 12-lead Holter monitor (CardioMem CM 3000-12BT; Getemed) in cardiomyopathy patients or a clinical electrophysiology workstation (CardioLab; GE Medical Systems) in control patients. The ECG recordings were downloaded for analysis of QRSA and TWA using custom software written in MATLAB (v2012b; MathWorks).

For each pacing rate, alternans was measured in the precordial ECG leads (V1–V6) using the spectral method[12] with custom software previously developed and validated by our group (see Data S1 for further details).[13,14] Alternans was not evaluated in the limb leads because of a greater potential for motion artifacts producing spurious results.[15] Moreover, the limb leads are all derived from leads I and II, unlike the precordial leads, which are all independent. The QRS onset, QRS end (ie, J point), and T-wave end were manually demarcated by an expert observer on the superimposed signal average ECGs of all 6 precordial leads. For each lead, QRSA and TWA were quantified over a 128-beat window that was incrementally shifted by 16 beats from the beginning to the end of the pacing rate. Bad beats, defined as those with prematurity >5% of the pacing cycle length or a correlation coefficient <90% compared with the average beat, were replaced with the window's average even or odd beat as appropriate.[16] Windows with >10% bad beats were excluded from analysis. For each remaining window, power spectra were computed for each sample point in the QRS and JT segment and summed to create an aggregate power spectrum for the QRS and T wave, respectively. The alternans mean noise (S_{NB}), magnitude (V_{alt}), and signal:noise ratio (k value) were obtained as follows:

$$S_{NB} = \sqrt{\text{mean}\left(\text{power}_{0.44-0.49}\right)}$$

$$V_{alt} = \sqrt{\text{power}_{0.5} - S_{NB}^2}$$

$$\text{k value} = \frac{\left(\text{power}_{0.5} - \text{mean}\left(\text{power}_{0.44-0.49}\right)\right)}{\sigma\left(\text{power}_{0.44-0.49}\right)}$$

where $\text{power}_{0.5}$ is the spectral power at 0.5 cycle/beat and $\text{power}_{0.44-0.49}$ is the spectral power corresponding to frequencies between 0.44 and 0.49 cycles/beat (ie, the noise band).

A 128-beat segment was classified as alternans positive if ≥2 precordial leads had a *k* value ≥3. Segments that did not meet these criteria were classified as alternans negative. Positive segments with a significant frequency peak (*k* ≥3) at 0.25 cycle/beat were considered respiratory confounders and excluded due to the potential generation of artifactual alternans by a harmonic frequency. Negative segments that had >3 leads with a S_{NB} >1 SD over the mean S_{NB} of all patients were excluded due to the potential masking of true alternans by noise. The alternans magnitude for a positive segment was defined as the maximum V_{alt} among the precordial leads with a *k* value ≥3, while those of the negative segments were set to zero.

Alternans Classification

Figure 1 provides a flowchart illustrating our QRSA/TWA classification scheme. A pacing rate was classified as alternans positive if there were ≥3 consecutive alternans positive segments; otherwise, the pacing rate was considered alternans negative. Individual alternans-positive segments among pacing rates classified as negative were considered spurious and thus reclassified as negative and reassigned an alternans magnitude of zero. Pacing rates with <3 viable analysis segments were excluded from analysis. The alternans magnitude for a pacing rate was defined as the maximum alternans magnitude from the nonexcluded segments. A patient was classified as QRSA positive (QRSA+) or TWA positive (TWA+) if any of their individual pacing rates were classified as QRSA+ or TWA+, respectively. The alternans magnitude for a patient was defined as the maximum alternans magnitude across all pacing rates. For comparison with prior clinical studies assessing the relationship between TWA and VA,[5,7,12] patients were also classified as being TWA nonnegative (TWA ≥1.9 μV) if (1) TWA was present with a magnitude ≥1.9 μV at pacing rates ≤110 bpm or (2) the pacing rate at 110 bpm was excluded from analysis and the pacing rate at 120 bpm was either also excluded or exhibited TWA with a magnitude ≥1.9 μV (ie, an indeterminate TWA test).

To study the interaction between QRSA and TWA, each pacing rate was classified into one of 4 mutually exclusive categories based on the presence or absence of QRSA and TWA at that rate: QRSA negative/TWA negative (QRSA–/TWA–), QRSA+/TWA–, QRSA–/TWA+, and QRSA+/TWA+. Each patient was then similarly classified based on the presence of these categories across the different pacing rates as follows: (1) patients who were QRSA–/TWA– at all rates were classified as QRSA–/TWA–, (2) patients with any rate classified as QRSA+/TWA– and no TWA+ rates were classified as QRSA+/TWA–, (3) patients with any rate classified as QRSA–/TWA+ and no QRSA+ rates were classified as QRSA–/TWA+, and (4) patients who were QRSA+/TWA+ at any rate or QRSA+/TWA– and QRSA–/TWA+ at different rates were classified as QRSA+/TWA+.

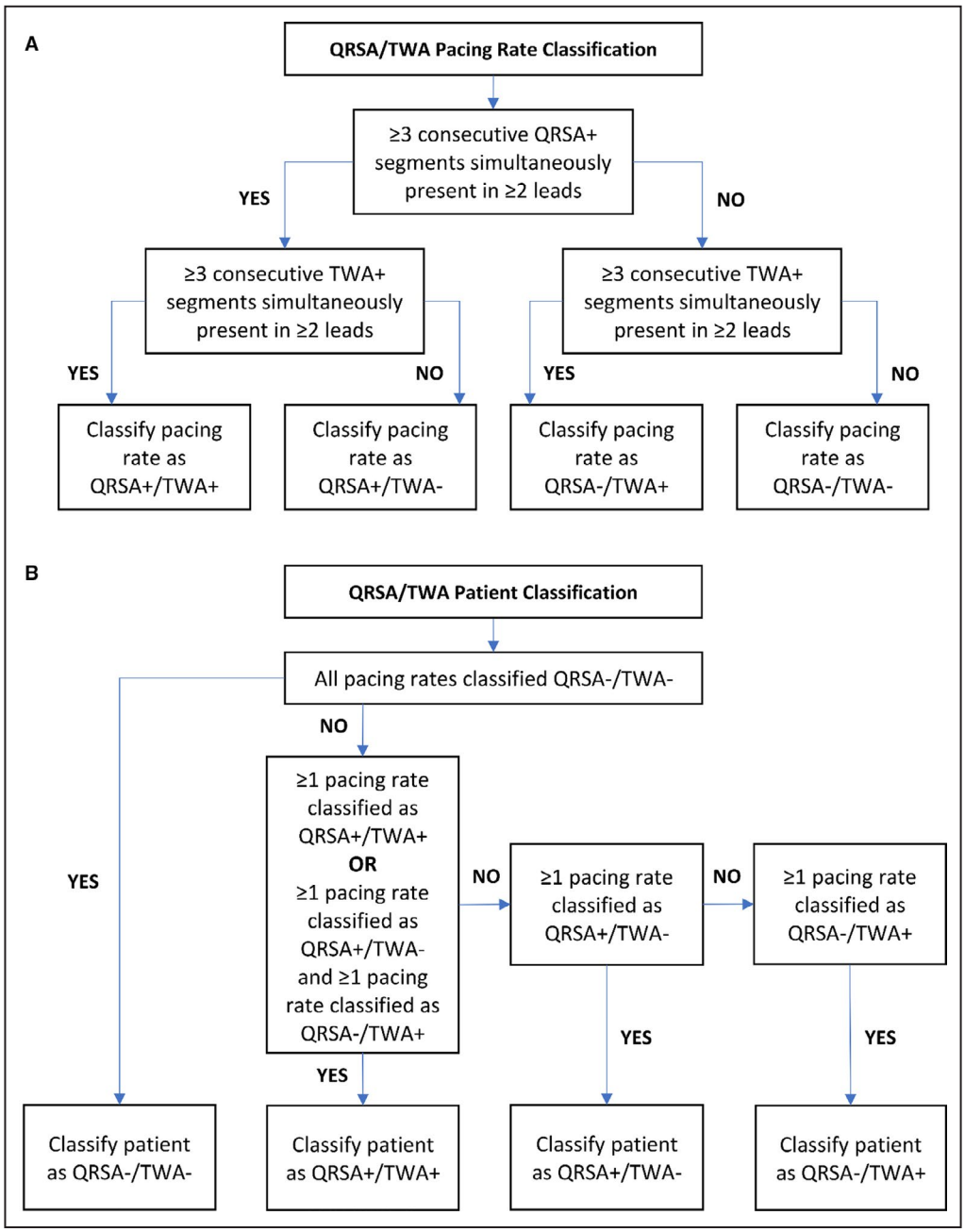

Figure 1. QRSA/TWA classification flowchart.
Flowcharts illustrating QRSA/TWA classification schemes used to classify the (**A**) individual pacing rates and (**B**) patients as QRSA−/TWA−, QRSA+/TWA−, QRSA−/TWA+ or QRSA+/TWA+. QRSA indicates QRS alternans; and TWA, T-wave alternans.

Long-Term Clinical Outcomes

Prophylactic ICD programming was standardized for all patients as follows: ventricular tachycardia (VT) monitor zone at 150 bpm (24 intervals or equivalent time); VT detection zone at 182 bpm (18 intervals or equivalent time) to deliver antitachycardia pacing followed by cardioversion shock; ventricular fibrillation detection zone at 250 bpm (18/24 intervals or equivalent time) to deliver ICD shock. SVT discriminators were enabled, and bradycardia pacing was set to VVI at 50 bpm. Patients were followed prospectively in the ICD clinic every 6 months for 3.5 years to evaluate the primary outcome of VA, which included appropriate ICD therapy or sustained VT below ICD detection. Patients with <12 months follow-up were excluded from analysis.

Statistical Analysis

Continuous variables are presented as mean±SD or median (interquartile range [IQR]), as appropriate. The Student *t* test or Mann-Whitney *U* test was used for

unpaired comparison of patients with and without clinical events. Categorical variables are presented as frequency or percentage and were compared by χ^2 or Fisher exact test, as appropriate. To control for excluded pacing studies and within-patient effects, linear mixed and logistic regression models with repeated measures were used to compare differences among the 3 pacing rates for continuous and categorical alternans metrics, respectively. The McNemar test was used to compare the shift in proportions for each QRSA/TWA category between pacing at 100 and 120 bpm.

Arrhythmia-free survival (freedom from sustained VT or appropriate ICD therapy) was determined for the alternans groups in the cardiomyopathy cohort using Kaplan–Meier analysis and compared with the log-rank test. Univariable and multivariable Cox regression analysis was used to further assess the predictive value of QRSA, TWA, and other candidate covariates. Regression results are presented as the hazard ratio (HR) and 95% CI. The multivariable models included covariates with a univariable significance level of $P<0.1$ and sex. Multicollinearity between potential predictor variables was considered to be present if the variance inflation factor for any variable was >3. Model goodness-of-fit and discrimination were assessed using the Gronnesby-Borgan test and Harrell C-statistic, respectively. All assumptions of the Cox proportional hazards regression model were verified.

All statistical analyses were performed using MATLAB (v8.0; MathWorks), SPSS (v20.0; IBM Corp), or Stata (v13; StataCorp). A 2-sided $P<0.05$ was considered statistically significant.

RESULTS

Patient Population

The study cohort included 100 patients (mean age, 62±11 years; 85% male) with ischemic (n=62) or nonischemic (n=38) cardiomyopathy and a mean LV ejection fraction of 27±7%. The control group comprised 6 patients (mean age, 45±20 years; 67% male) with a mean LV ejection fraction of 57±5%. None of the control patients were found to have inducible VA during electrophysiology study or subsequently received an ICD.

Microvolt QRS and T-Wave Alternans

In the control group, all 6 patients had at least 2 ventricular pacing rates completed such that there were 5, 4, and 6 rates available for alternans assessment at 100, 110, and 120 bpm, respectively. None of the control pacing rates were excluded, and no QRSA or TWA was detected in any patient at any rate. In the cardiomyopathy group, 5 patients were excluded because of excessive ectopic or fused beats at all rates, which made alternans assessment unreliable. Among the remaining 95 patients, there were 9 (9%), 10 (11%), and 10 (11%) pacing rates excluded at 100, 110, and 120 bpm, respectively. Of these 32 excluded pacing rates, 21 were due to excessive ectopy, 4 were due to excessive alternans noise, and 4 were due to the patient's inability to tolerate the pacing rate for 3 minutes. Study exclusions are illustrated in Figure S1. QRSA was detected in 44% of patients, with a median alternans magnitude of 9.7 μV (IQR, 5.2–16.7 μV) among a median of 33% (IQR, 14%–48%) positive segments per pacing rate. TWA was detected in 48% of patients with a median alternans magnitude of 8.0 μV (IQR, 4.3–12.0 μV) among a median of 38% (IQR, 10%–54%) positive segments per pacing rate. QRSA characteristics did not change with rate. In contrast, the number of TWA+ pacing rates, percentage of TWA+ segments, and TWA magnitude all increased with rate (Table 1).

The mean alternans noise in cardiomyopathy patients was small (median S_{NB}, <4 μV) in all precordial leads for both QRSA and TWA (Table S1). There was no difference between cardiomyopathy and control patients in the QRSA S_{NB} (V1: 3.4±1.7 versus 2.4±1.0, $P=0.04$; V2: 4.4±2.9 versus 4.0±2.3, $P=0.62$; V3: 4.4±3.4 versus 4.3±2.8, $P=0.95$; V4: 4.6±3.6 versus 4.0±2.3, $P=0.60$; V5: 3.7±2.3 versus 3.8±1.9, $P=0.84$; V6: 3.1±2.0 versus 2.5±1.2, $P=0.35$) or TWA S_{NB} (V1: 2.7±1.5 versus 1.9±0.8, $P=0.05$; V2: 3.4±2.3 versus 2.8±1.5, $P=0.41$; V3: 3.6±3.3 versus 3.1±1.7, $P=0.55$; V4: 3.7±3.0 versus 3.1±1.4, $P=0.53$; V5: 3.1±2.0 versus 2.8±1.0, $P=0.66$; V6: 2.7±1.8 versus 2.0±0.7, $P=0.18$).

Interaction of QRSA and TWA

The proportions of patients classified as QRSA–/TWA–, QRSA+/TWA–, QRSA–/TWA+, and QRSA+/TWA+ were 38%, 14%, 18%, and 31%, respectively.

Table 1. QRSA/TWA Rate Relation (N=95)

	100 bpm (n=86)	110 bpm (n=85)	120 bpm (n=85)	*P* Value
QRSA				
Positive studies, n (%)	22 (26)	26 (31)	25 (29)	0.717*
Positive segments, %	16±3	17±3	20±4	0.607†
Alternans magnitude, μV	2.5±0.6	2.7±0.6	3.4±0.7	0.534†
TWA				
Positive studies, n (%)	14 (16)	22 (26)	39 (46)	<0.001*
Positive segments, %	11±3	17±4	29±4	0.001†
Alternans magnitude, μV	1.4±0.4	2.2±0.5	4.7±1.0	0.006†

Continuous data presented as mean±SE. QRSA indicates QRS alternans; and TWA, T-wave alternans.

*Statistical significance assessed using repeated measures logistic regression.

†Statistical significance assessed using linear mixed model with repeated measures.

Among the QRSA+/TWA+ patients, only 2 exhibited QRSA+/TWA– and QRSA–/TWA+ at different rates without being QRSA+/TWA+ at any rate. Table S2 illustrates the rate-dependent interactions of QRSA and TWA. When comparing pacing at 100 to 120 bpm, the proportion of QRSA–/TWA+ studies increased from 5% to 24% (P=0.001), and the proportion of QRSA+/TWA+ studies trend toward an increase of 12% to 22% (P=0.077). In contrast, the proportion of studies with QRSA+/TWA– remained constant (14% versus 7%, P=0.424), further highlighting the rate-independent behavior of QRSA.

Because large-magnitude action potential alternans is associated with both QRSA and larger magnitude TWA,[1] we evaluated QRSA and TWA magnitudes when they occurred in isolation (ie, QRSA+/TWA– and QRSA–/TWA+) and simultaneously (ie, QRSA+/TWA+). Compared with pacing studies that were QRSA+/TWA+, the median QRSA and TWA magnitudes were significantly less in pacing studies that were QRSA+/TWA– (QRSA magnitude: 10.4 μV [IQR, 6.9–16.7 μV] versus 5.1 μV [IQR, 3.7–7.3 μV], P=0.001) and QRSA–/TWA+ (TWA magnitude: 7.5 μV [IQR, 4.3–11.8 μV] versus 5.4 μV [IQR, 3.2–7.2 μV], P=0.007), respectively.

Figures 2 through 4 illustrate QRSA and TWA during low and high pacing rates for 3 different patients who were classified as QRSA+/TWA–, QRSA–/TWA+, and QRSA+/TWA+, respectively (see also Figure S2). QRSA magnitudes remained similar at low and high pacing rates in the QRSA+/TWA– and QRSA+/TWA+ patients, whereas the TWA magnitudes increased with pacing rate in the QRSA–/TWA+ and QRSA+/TWA+ patients. The magnitude of the QRSA and TWA in the patient who was QRSA+/TWA+ was also greater than that of the patients who were QRSA+/TWA– and QRSA–/TWA+, respectively.

Relationship to VAs

Ninety-three cardiomyopathy patients were followed for a median of 42 months (IQR, 22–42 months), and 18 (19%) experienced the primary outcome of VA after a median of 18 months (IQR, 8–30 months), whereas 2 patients were excluded because of nonarrhythmic death before 12 months of follow-up. Among the 93 patients, 17 (18%) were lost to follow-up, 7 (8%) had nonarrhythmic deaths, and 1 (1%) had their ICD explanted before the completion of the 3.5-year follow-up period. Among the 18 patients who experienced a VA event, 16 patients had monomorphic VT (mean heart rate, 205±30 bpm) and 2 had polymorphic VT or ventricular fibrillation (mean heart rate, 288±39 bpm). The VA events were successfully treated by ICD shock and antitachycardia pacing in 10 and 5 patients, respectively. The remaining 3 patients had self-limiting sustained VTs in the VA monitor zone and did not receive treatment from their device.

The baseline clinical characteristics of VA+ and VA– patients are presented in Table 2. Patients who were VA+ had greater native QRS duration (QRSd) compared with VA– patients (QRSd: 138±23 versus 113±26, P<0.001; QRSd ≥120 ms: 78% versus 36%, P=0.003). No other differences in clinical characteristics were observed between VA+ and VA– patients.

Table 3 compares QRSA and TWA characteristics between VA+ and VA– patients. Although there was no difference in TWA characteristics between the VA groups, the proportion of patients with QRSA (78% versus 37%, P=0.003) and the QRSA magnitudes (3.9 μV [IQR, 2.3–10.7 μV] versus 0.0 μV [IQR, 0.0–7.2 μV], P=0.036) were greater in VA+ patients. There was also a trend toward a greater percentage of QRSA+ segments in VA+ patients (12% [IQR, 4%–32%] versus 0% [IQR, 0%–33%], P=0.06). When considering the individual QRSA/TWA categories, there was a lesser proportion of patients with no alternans (QRSA–/TWA–: 11% versus 45%, P=0.007) but greater proportion of patients with isolated QRSA (QRSA+/TWA–: 44% versus 7%, P<0.001) in the VA+ group. However, there was no difference in the proportion of patients with isolated TWA (ie, QRSA–/TWA+) or simultaneous QRSA and TWA (ie, QRSA+/TWA+). No difference was observed in QRSA or TWA noise between VA+ and VA– patients (Table S1).

Kaplan–Meier event-free survival curves for QRSA, TWA, and TWA ≥1.9 μV and among the 4 QRSA/TWA patient categories are presented in Figure 5. After 3.5 years of follow-up, QRSA– patients had greater freedom from VA than QRSA+ patients (P=0.005), whereas VA outcome was similar between TWA+ versus TWA– patients (P=0.677) and TWA ≥1.9 μV versus TWA <1.9 μV patients (P=0.34). Among the QRSA/TWA categories, patients who were QRSA–/TWA– (P<0.001), QRSA–/TWA+ (P=0.016), and QRSA+/TWA+ (P=0.004) each had greater freedom from VA than patients who were QRSA+/TWA–. There was no difference in survival outcomes between any of the other categories.

Previously established clinical predictors of VA and the alternans metrics were evaluated with Cox regression analysis (Table 4). Univariable predictors of VA included age (per 5 years: HR, 1.24 [95% CI, 0.97–1.58], P=0.092), QRSd (per 10 ms: HR, 1.28 [95% CI, 1.10–1.48], P=0.001), QRSd >120 ms (HR, 5.25 [95% CI, 1.72–15.99], P=0.004), and QRSA+ (HR, 4.35 [95% CI, 1.43–13.23], P=0.010). Multivariable analysis of the univariable predictors (P<0.1) and sex revealed QRSA+ to be the strongest predictor of VA in a model including QRSd as a continuous variable (HR, 3.91 [95% CI, 1.20–12.68], P=0.023; goodness-of-fit test P=0.38; C-statistic, 0.77 [95% CI, 0.67–0.87]) and another

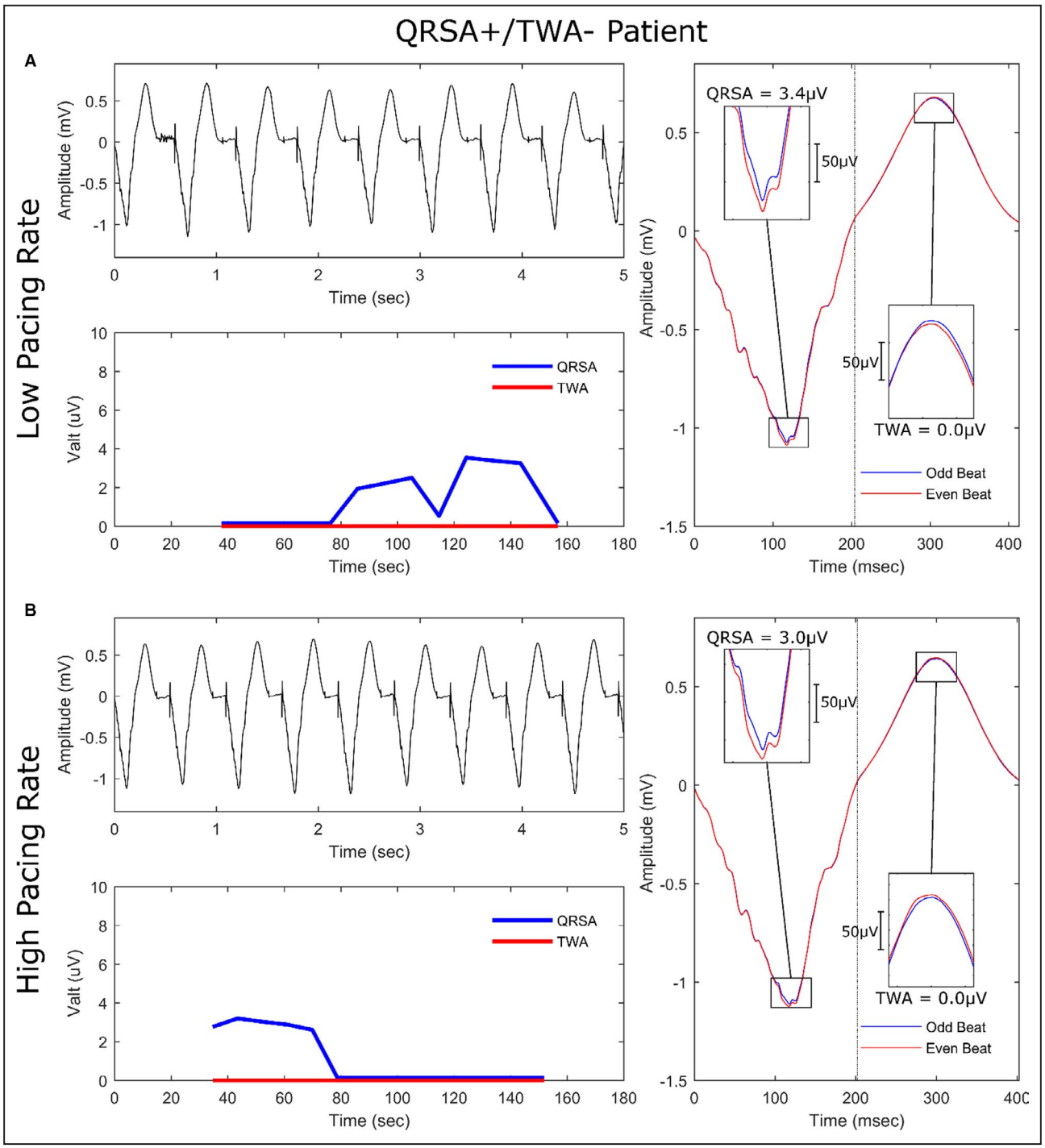

Figure 2. QRSA and TWA at low and high pacing rates in a QRSA+/TWA– patient.
Illustration of microvolt QRSA and TWA in a QRSA+/TWA– patient during (**A**) low and (**B**) high pacing rates. Upper left panel illustrates a representative 5-second ECG from lead V5 during the 3-minute ventricular pacing study. Lower left panel illustrates QRSA (blue) and TWA (red) magnitudes for each 128-beat alternans analysis window in the 3-minute pacing study. Right panel illustrates superimposed mean odd (blue) and even (red) beats from a representative 128-beat analysis window to highlight the low-magnitude scale of alternans on the ECG. QRSA magnitudes remain similar at the low and high rates, whereas TWA is not present at either rate. QRSA indicates QRS alternans; and TWA, T-wave alternans.

including QRSd ≥120 ms as a dichotomous variable (HR, 4.55 [95% CI, 1.46–14.21], *P*=0.009; goodness-of-fit test *P*=0.68; C-statistic, 0.76 [95% CI, 0.65–0.86]). Multicollinearity was not observed (variance inflation factor <3) between any of the variables included in the multivariable models.

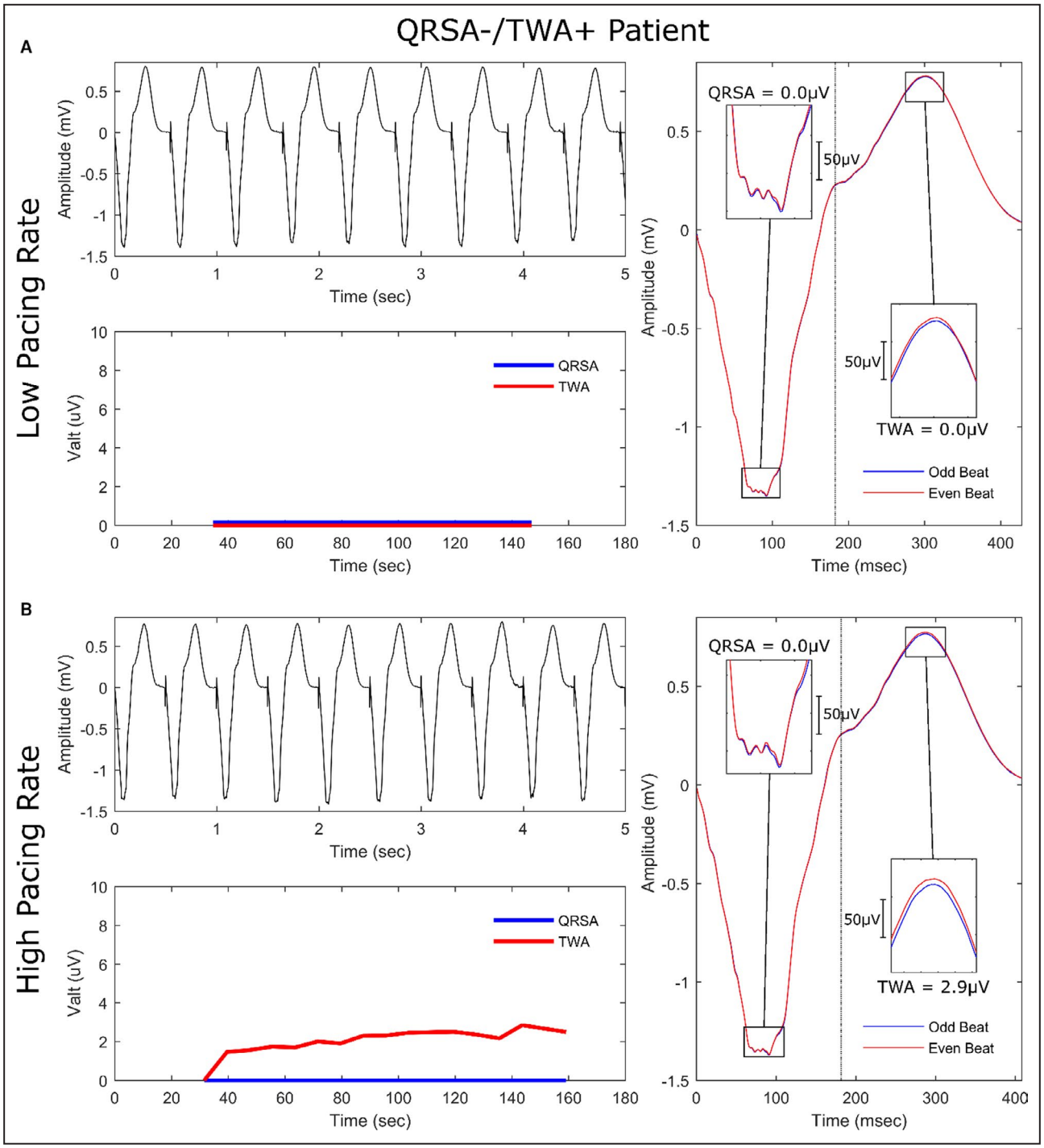

Figure 3. QRSA and TWA at low and high pacing rates in a QRSA−/TWA+ patient.
Illustration of microvolt QRSA and TWA in a QRSA−/TWA+ patient during (**A**) low and (**B**) high pacing rates. Upper left panel illustrates a representative 5-second ECG from lead V4 during the 3-minute ventricular pacing study. Lower left panel illustrates QRSA (blue) and TWA (red) magnitudes for each 128-beat alternans analysis window in the 3-minute pacing study. Right panel illustrates superimposed mean odd (blue) and even (red) beats from a representative 128-beat analysis window to highlight the low-magnitude scale of alternans on the ECG. TWA magnitudes increase from the low to high rate, whereas QRSA is not present at either rate. QRSA indicates QRS alternans; and TWA, T-wave alternans.

The clinical characteristics of QRSA− and QRSA+ patients are presented in Table S3. A greater proportion of QRSA− patients had renal dysfunction compared with QRSA+ patients (41% versus 10%, P=0.001). Although there was no difference in the proportion of patients with QRSd >120 ms between QRSA− and QRSA+ patients (41% versus 48%, P=0.533), patients with QRSA+ had greater QRSd (124±30 versus

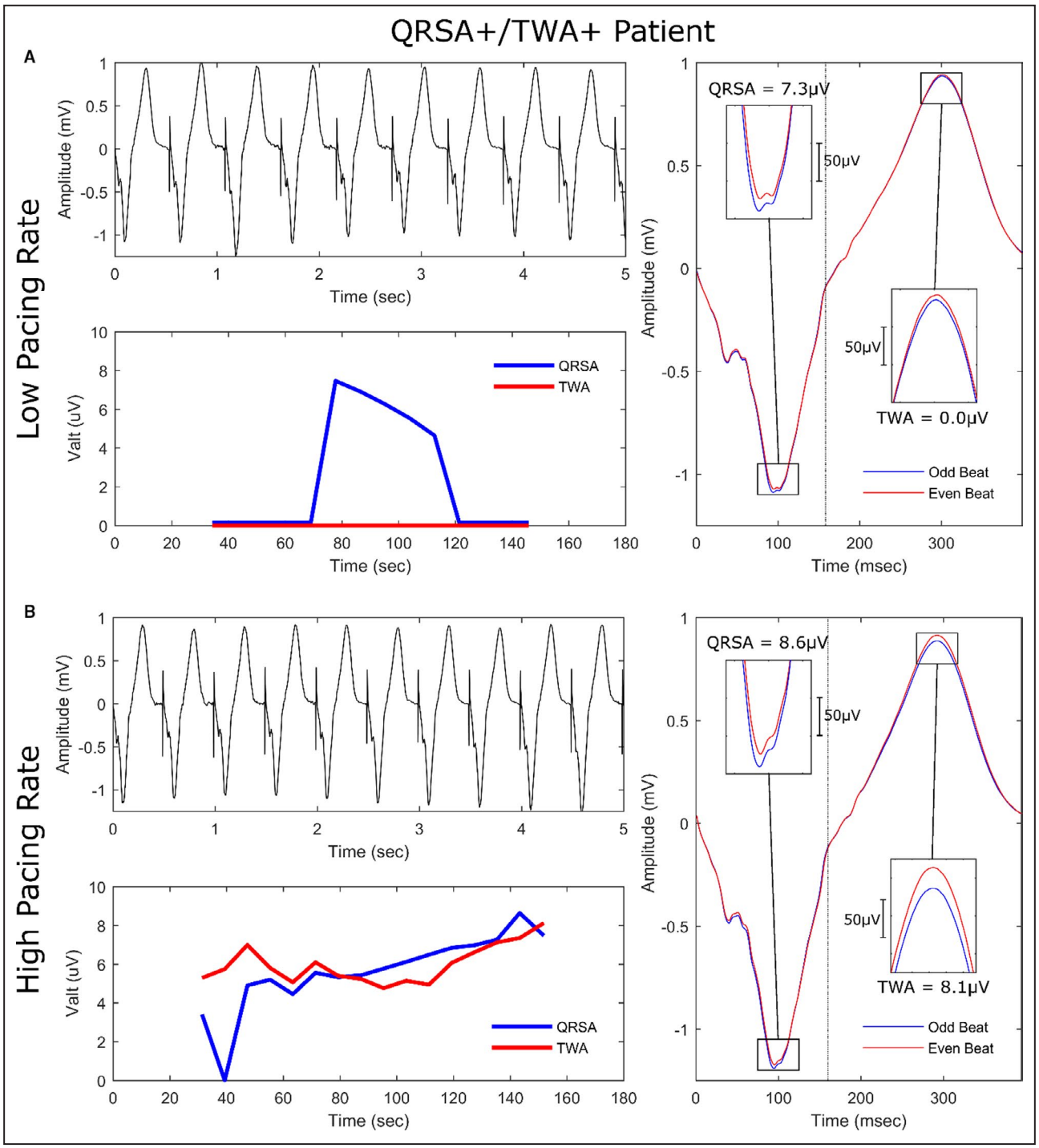

Figure 4. QRSA and TWA at low and high pacing rates in a QRSA+/TWA+ patient.
Illustration of microvolt QRSA and TWA in a QRSA+/TWA+ patient during (**A**) low and (**B**) high pacing rates. Upper left panel illustrates a representative 5-second ECG from lead V4 during the 3-minute ventricular pacing study. Lower left panel illustrates QRSA (blue) and TWA (red) magnitudes for each 128-beat alternans analysis window in the 3-minute pacing study. Right panel illustrates superimposed mean odd (blue) and even (red) beats from a representative 128-beat analysis window to highlight the low-magnitude scale of alternans on the ECG. QRSA magnitudes remain similar at the low and high rates, whereas TWA magnitudes increase with rate. Sample QRS and T-wave power spectra of a 128-beat segment from the high rate study are presented in Figure S2. QRSA indicates QRS alternans; and TWA, T wave alternans.

113±24, *P*=0.043). No other differences in clinical characteristics were observed between patients with and without QRSA. Among the QRSA+ patients, those with QRSA+/TWA+ had lower LV ejection fraction than QRSA+/TWA– patients (25±6% versus 29±6%, *P*=0.037).

Table 2. Clinical Variables and Arrhythmic Outcomes

	All Patients* (n=93)	VA– (n=75)	VA+ (n=18)	*P* Value
Age, y	62±11	62±11	66±6	0.128
Male sex, n (%)	80 (86)	65 (87)	15 (83)	0.711
LVEF, %	27±7	28±7	26±7	0.316
LVEF <35%, n (%)	78 (84)	63 (84)	15 (83)	1.000
Etiology of cardiomyopathy, n (%)				1.000
Ischemic	59 (63)	47 (63)	12 (67)	
Nonischemic dilated	34 (37)	28 (37)	6 (33)	
NYHA functional class, n (%)				0.676
I	33 (36)	25 (33)	8 (44)	
II	41 (44)	33 (44)	8 (44)	
III	18 (19)	16 (21)	2 (11)	
IV	1 (1)	1 (1)	0 (0)	
Comorbidities, n (%)				
Hypertension	47 (51)	36 (48)	11 (61)	0.432
Diabetes mellitus	40 (43)	31 (41)	9 (50)	0.599
Prior revascularization	48 (52)	37 (49)	11 (61)	0.437
Renal dysfunction†	25 (27)	19 (25)	6 (33)	0.557
Medications, n (%)				
β-Blocker	88 (95)	70 (93)	18 (100)	0.579
ACEI/ARB	84 (90)	68 (91)	16 (89)	1.000
Diuretic	70 (75)	56 (74)	14 (78)	1.000
Class III antiarrhythmic	6 (7)	5 (7)	1 (6)	1.000
Calcium channel blockers	2 (2)	2 (3)	0 (0)	1.000
Lipid-lowering agents	72 (77)	57 (76)	16 (83)	0.754
Antiplatelet agents	61 (66)	50 (67)	11 (61)	0.783
Traditional ECG parameters				
Resting heart rate, bpm	68±11	68±11	66±11	0.632
QT interval, ms	426±40	426±40	427±43	0.900
QTc interval, ms	450±34	450±34	447±35	0.709
QRSd, ms	118±27	113±26	138±23	<0.001
QRSd ≥120 ms, n (%)	41 (44)	27 (36)	14 (78)	0.003
LBBB, n (%)	17 (18)	11 (15)	6 (33)	0.089

Continuous data presented as mean±SD. ACEI/ARB indicates angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker; bpm, beats per minute; LBBB, left bundle-branch block; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; QRSd, QRS duration; VA, ventricular tachyarrhythmia.

*Patients with ≥12 months follow-up.

†eGFR <61 mL/min per 1.73 m^2.

DISCUSSION

In this prospective study, our main findings regarding microvolt QRSA induced with ventricular pacing at 100 to 120 bpm are as follows: (1) QRSA is prevalent in 44% of cardiomyopathy patients but is not present in those with preserved ventricular function; (2) the prevalence and magnitude of QRSA does not exhibit rate dependence, unlike microvolt TWA; (3) QRSA can occur without TWA in 14% of cardiomyopathy patients; and (4) QRSA, when coupled with TWA, manifests greater QRSA magnitude than QRSA alone. In addition, we demonstrated that QRSA independently predicts late occurrence of VA, whereas TWA does not, and the greatest risk of VA is in those QRSA+ patients without TWA. These findings have not been described previously in patients with cardiomyopathy and provide novel insights into the prevalence, coupling, and rate dependence of electrical alternans and their prognostic relevance.

Basis for Microvolt QRSA and TWA

The mechanism of TWA has been elucidated from optically mapped, normal, guinea pig explanted hearts during incremental ventricular pacing. In these studies, rapid pacing-induced intracellular calcium alternans

Table 3. Alternans and Arrhythmic Outcomes

	All Patients* (n=93)	VA– (n=75)	VA+ (n=18)	*P* Value
QRSA metrics				
QRSA+ study, n (%)	42 (45)	28 (37)	14 (78)	0.003
QRSA+ segments, %	0 (0–30)	0 (0–33)	12 (4–32)	0.060
QRSA magnitude, μV	0.0 (0.0–7.5)	0.0 (0.0–7.2)	3.9 (2.3–10.7)	0.036
TWA metrics				
TWA+ study, n (%)	44 (47)	35 (48)	8 (44)	1.000
TWA ≥1.9μV study, n (%)	28 (30)	24 (32)	4 (22)	0.570
TWA+ segments, %	0 (0–33)	0 (0–33)	0 (0–9)	0.517
TWA magnitude, μV	0.0 (0.0–7.5)	0.0 (0.0–8.5)	0.0 (0.0–4.5)	0.744
QRSA/TWA classification, n (%)				<0.001†
QRSA–/TWA–	36 (39)	34 (45)	2 (11)	0.007‡
QRSA+/TWA–	13 (14)	5 (7)	8 (44)	<0.001‡
QRSA–/TWA+	15 (16)	13 (17)	2 (11)	0.727
QRSA+/TWA+	29 (31)	23 (31)	6 (33)	1.000

Continuous data presented as median (interquartile range). QRSA indicates QRS alternans; TWA, T-wave alternans; and VA, ventricular tachyarrhythmia.
*Patients with ≥12-month follow-up.
†χ^2 test.
‡Individual category statistical significance at Bonferroni corrected $P<0.0125$.

gave rise to action potential alternans, which manifested on the surface ECG as TWA.[1–3] TWA magnitude is rate dependent, and its heart rate onset is lower in cardiomyopathy than normal hearts because of abnormalities in sarcolemma–calcium cycling proteins.[17] Our findings also demonstrated a strong rate-dependence of TWA in cardiomyopathy patients during ventricular pacing of 100 to 120 bpm.

In contrast, the mechanism of QRSA is less well understood. In the same explanted guinea pig hearts during very rapid pacing, low-magnitude visible QRSA develops as a result of larger magnitude action potential alternans, but this is also associated with visible TWA.[1] However, the absence of TWA in 14% of our patients who manifested QRSA suggests that calcium alternans may not be a relevant mechanism. Instead, we propose that alternans in His-Purkinje and/or myocardial (HPM) conduction may be a more plausible mechanism. This process has been suggested as a cause of visible QRSA during rapid SVT in some patients with structurally normal hearts.[9] In this study, QRSA was dependent on the SVT rate and could be reproduced with abrupt, rapid atrial pacing.[10] Tchou et al[11] demonstrated retrograde His-Purkinje alternans (ie, alternating retrograde His-Purkinje relative refractory period) without myocardial alternans (ie, no alternating ventricular effective refractory period) during abrupt, rapid ventricular pacing in patients with normal QRSd and normal HV intervals. In our cardiomyopathy patients, microvolt QRSA was evident at significantly lower heart rates compared with these SVT patients, which may be the consequence of HPM conduction disease. Moreover, our patients with QRSA had longer QRSd than those without QRSA, suggesting that more severe HPM conduction disease may be causal. HPM conduction, including transseptal right ventricular to LV conduction time, is prolonged in cardiomyopathy patients because of intramural scar and/or functional lines of block.[18] Alternation in His-Purkinje conduction or transseptal conduction from functional block may result in QRSA due to subtle conduction detours into the left ventricle on every alternate beat during right ventricular pacing, as shown in Figure 6.

It is unclear why our patients did not manifest QRSA rate dependence if the retrograde HPM conduction is pathogenic; however, rate dependence might have occurred if pacing rates >120 bpm were investigated. Although QRSA did not manifest rate dependence, its magnitude was greater in the presence of TWA. This finding is not unexpected because ventricular depolarization is coupled to repolarization, so a sufficiently large change in the QRS vector of depolarization should alter the T-wave vector of repolarization.[19] Therefore, it is possible that patients with both QRSA and TWA had greater alternation in ventricular activation from retrograde His-Purkinje–based alternans and/or from greater myocardial mass alternans.[20,21]

Clinical Implications

Action potential alternans provides the substrate for reentry when the alternans is spatially discordant.[1,12] In this situation, adjacent regions are alternating out of phase, such that long and short action potentials

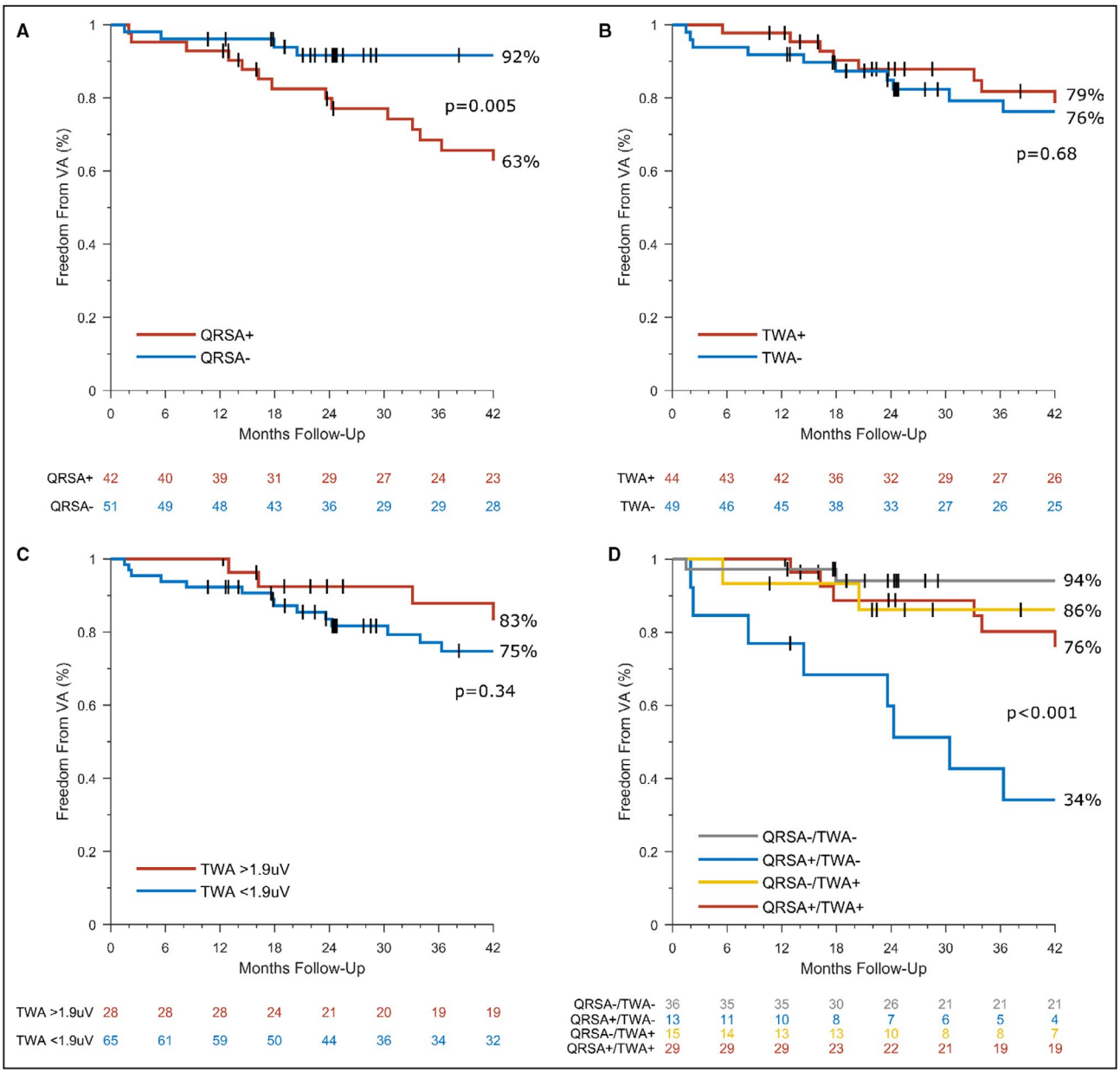

Figure 5. Kaplan–Meier survival curves for VA events.
Kaplan–Meier survival curves for the end point of VA events stratified by (**A**) QRSA (**B**) TWA, (**C**) clinically significant TWA (>1.9 μV), and (**D**) the combined QRSA/TWA classification. QRSA indicates QRS alternans; TWA, T-wave alternans; and VA, ventricular tachyarrhythmia.

are juxtaposed, which leads to conduction block into the region with the longer action potential. Early clinical studies in patients with cardiomyopathy showed that microvolt TWA surges precede and predict late VA[5–8]; however, subsequent larger clinical trials did not confirm these findings.[22] Our study also did not show any predictive accuracy for late VA with TWA, whether defined by V_{alt} >0 μV or a more conservative cut point of V_{alt} >1.9 μV, as used in clinical TWA reports.[5,7,12]

In contrast, the presence of microvolt QRSA (V_{alt} >0 μV) independently increases the risk of VA by 4-fold in our cardiomyopathy patients. The VA risk was greatest in patients with QRSA but without TWA, which is not intuitive because QRSA magnitudes were lower in these patients compared with those with both QRSA and TWA. However, if HPM alternans is indeed an important mechanism in QRSA, then our findings may suggest that spatially localized HPM alternans, which may cause QRSA but not TWA, is more arrhythmogenic than more diffuse HPM alternans. We speculate that localized HPM alternans is occurring in discrete, heterogenous ventricular scar as a result of alternating exits into healthy myocardium from functional block in protected channels, as

Table 4. Cox Regression Analysis for Prediction of Arrhythmic Events (N=93)*

	Univariable Analysis		Multivariable Model 1†		Multivariable Model 2‡	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Age, per 5 y	1.24 (0.97–1.58)	0.092	1.31 (0.95–1.79)	0.101	1.27 (0.94–1.73)	0.125
Male sex	0.83 (0.24–2.86)	0.763	0.71 (0.18–2.83)	0.626	0.91 (0.23–3.62)	0.888
LVEF. per 5%	0.87 (0.62–1.22)	0.428	…	…	…	…
LVEF <35%	0.92 (0.27–3.17)	0.892	…	…	…	…
QRSd, per 10 ms	1.28 (1.10–1.48)	0.001	1.21 (1.03–1.41)	0.021	…	…
QRSd >120 ms	5.25 (1.72–15.99)	0.004	…	…	4.10 (1.33–12.61)	0.014
QRSA+	4.35 (1.43–13.23)	0.010	3.91 (1.20–12.68)	0.023	4.55 (1.46–14.21)	0.009
TWA+	0.82 (0.32–2.08)	0.677	…	…	…	…

HR indicates hazard ratio; LVEF, left ventricular ejection fraction; QRSA, QRS alternans; QRSd, QRS duration; and TWA, T-wave alternans.
*Patients with ≥12-month follow-up.
†Model 1: Goodness-of-fit test *P*=0.38; C-statistic, 0.77 (95% CI, 0.67–0.87).
‡Model 2: Goodness-of-fit test *P*=0.68; C-statistic, 0.76 (95% CI, 0.65–0.86).

illustrated in Figure 6. Such heterogeneous myocardial scar in animal infarct models has been shown to be arrhythmogenic when functional conduction block in protected channels initiates reentry.[23,24] A similar phenomenon has also been described during atrial tachycardia, in which alternating functional block in different limbs of the reentrant circuit causes cycle-length alternans.[25]

Our multivariable modeling also revealed that QRSd was an independent predictor of VA, but the association was less strong than QRSA. Although there is a relationship between QRSA and QRSd, they are not colinear but rather provide independent prognostic information. Therefore, QRSA may refine the phenotyping of HPM conduction disease in patients with QRS prolongation who may be at risk of sudden death. The utility of QRSA testing with ventricular pacing to risk-stratify patients with cardiomyopathy for prophylactic ICD therapy warrants further study in a larger multicenter cohort.

Prior Studies on QRSA

Few clinical studies have evaluated visible and microvolt QRSA. Brembilla-Perrot et al[26] showed large-magnitude QRSA during rapid ventricular pacing, in the setting of dual AV node physiology, 2:1 VA conduction block, and 2:1 nodal echo beats. In this example of retrograde His-Purkinje/AV-node conduction alternans, both visible QRSA and TWA were observed. A few series have demonstrated low-magnitude, rate-dependent QRSA in patients with rapid SVT and normal ventricular function.[10,27] Rosenbaum et al[4] was the first to evaluate microvolt QRSA and TWA using the spectral method in a mixed patient population with normal and depressed LV function that presented with syncope or VA. QRSA was less prevalent and of lower magnitude than TWA. When tested in a subgroup of 10 patients, QRSA also exhibited a rate-dependent increase, whereas TWA remained constant. Although TWA predicted both inducible VA and VA-free survival, QRSA was not a significant predictor of inducibility, and its relation to survival was not evaluated. These findings differ from our study possibly because of the patient characteristics and the use of atrial pacing at a single rate of 100 bpm to assess QRSA.

Limitations

Several limitations should be acknowledged. Foremost, QRSA and TWA were not assessed during atrial pacing or exercise stress testing, which physiologically engages the HPM system. Instead, ventricular pacing was performed to optimize QRST signal quality, minimize false-negative alternans detection from excessive noise, and reduce the likelihood of excluded studies due to atrioventricular nodal Wenckebach, which is common in cardiomyopathy patients on β-blocker therapy. However, TWA assessment using ventricular pacing has been shown to yield concordant results compared with atrial pacing.[28,29] Second, clinical TWA testing was not performed with proprietary skin electrodes or the Frank lead configuration, which may limit signal detection and prognostic accuracy.[12] However, the clinical definition of TWA was otherwise used, and careful skin preparation and motionless ECG sampling during ventricular pacing ensured low-noise recording conditions. Third, the role of HPM alternans in the pathogenesis of microvolt QRSA and its relation to TWA was not verified with high-resolution intracardiac activation mapping. Ventricular pacing rates >120 bpm would also improve the assessment of QRSA rate dependence, but this was not feasible in our patients with depressed cardiac reserve. Fourth, the role of other potential mechanisms for electrical alternans, such as the Brody effect, was not investigated. The Brody effect describes visible QRSA with TWA from

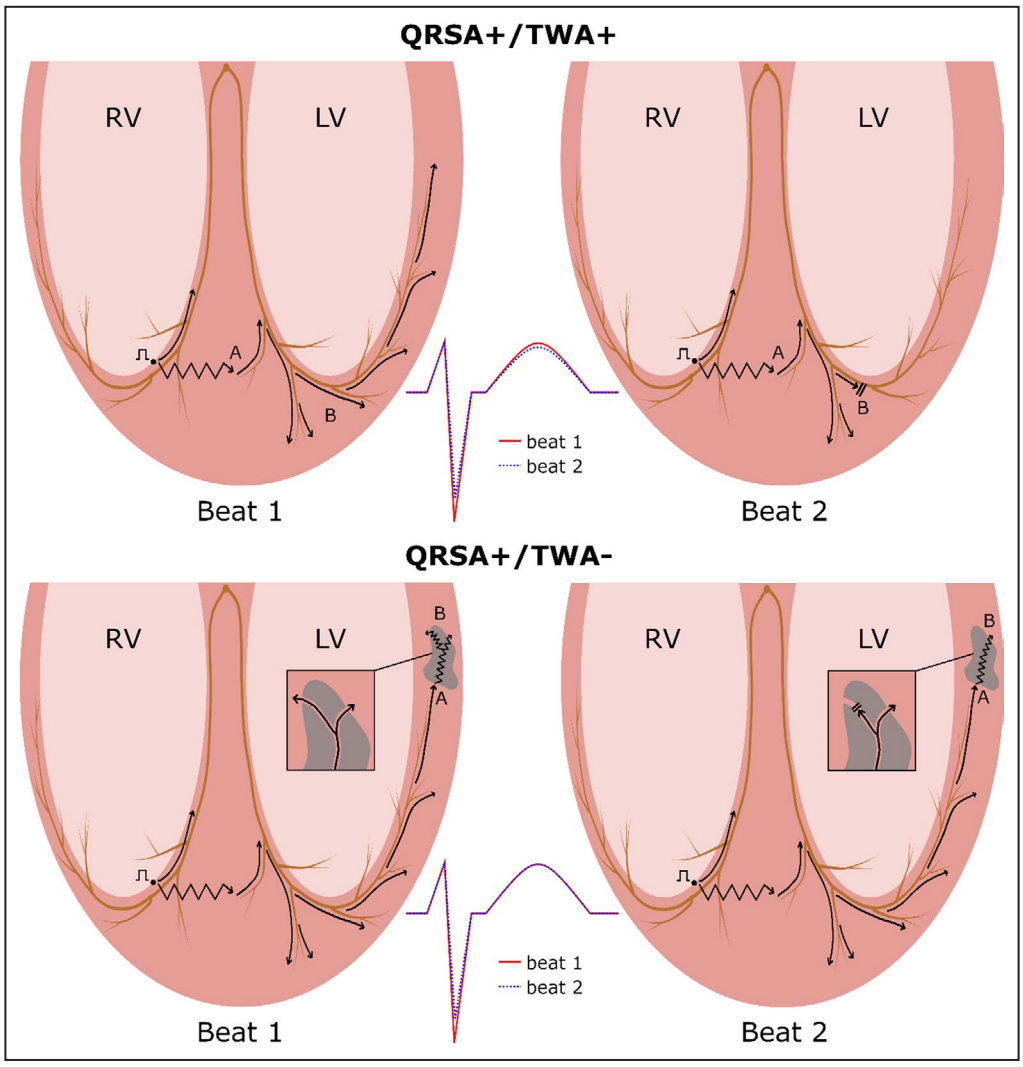

Figure 6. HPM conduction alternans as a potential mechanism of QRSA during RV pacing. Diagrammatic illustration of 2 possible scenarios in which HPM conduction alternans could generate microvolt QRSA during RV pacing. The upper panel illustrates distal His-Purkinje alternans. In beat 1 (left) and beat 2 (right), the activating wave front travels transseptally from the RV apical pacing site and conducts into the distal left bundle branch (**A**). Although the wave front exits broadly from the interconnected Purkinje fibers in beat 1, it encounters a functional block and can only exit a fraction of Purkinje fiber in beat 2 (**B**). This produces diffuse HPM alternans affecting a relatively large mass of myocardium, which may result in larger magnitude QRSA with TWA. In contrast, the lower panel illustrates myocardial alternans in a heterogenous scar. In beat 1 (left) and beat 2 (right), the activating wave front enters a common protected channel within the scar (**A**). Although the wave front exits from 2 protected channels in the scar on beat 1, it encounters a functional block in one of the channels on beat 2 (**B**). This produces localized myocardial alternans affecting a small mass of myocardium, which may produce smaller magnitude QRSA without TWA. This heterogeneous scar may also be arrhythmogenic if functional block in one of the protected channels causes reentrant ventricular tachycardia. HPM indicates His-Purkinje and/or myocardial; QRSA, QRS alternans; RV, right ventricular; and TWA, T-wave alternans.

alternating ventricular volumes due to severe LV systolic dysfunction.[30,31] This phenomenon may be relevant in our QRSA+/TWA+ subgroup, which had worse LV dysfunction and a lower risk of VA than QRSA+/TWA– patients. Finally, our sample size and number of VA events are not sufficient to establish a risk model, although this was not the primary goal of the study.

CONCLUSIONS

Microvolt QRSA induced by ventricular pacing is prevalent in patients with cardiomyopathy and can exist independently of microvolt TWA. Microvolt QRSA is not rate dependent between 100 and 120 bpm but is associated with QRS prolongation, suggesting HPM conduction alternans as a putative mechanism. Microvolt QRSA

independently increases the risk of late VA 4-fold and represents a novel risk marker in cardiomyopathy patients. Future studies are warranted to understand the pathogenesis of QRSA, its relation to VA, and its utility as a risk stratifier in patients who are eligible for prophylactic ICD.

ARTICLE INFORMATION

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Disclosures

None.

Supplementary Materials

Data S1
Tables S1–S3
Figures S1–S2

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SUPPLEMENTAL MATERIAL

Data S1.

SUPPLEMENTAL METHODS

Details of Pre-processing and Spectral Method for Alternans Analysis

For each lead, QRS and T wave alternans were quantified over consecutive 128-beat windows which were incrementally shifted by 16 beats from the beginning to the end of the pacing rate. To obtain an initial template QRST complex, an expert observer manually demarcated the QRS onset, QRS end (i.e. J point) and T wave end on the superimposed 3-minute signal average ECGs of all six precordial leads. Baseline wander was removed from each lead by subtracting an interpolated cubic spline fit to an iso-electric point prior to each QRST complex. The individual beats were then aligned by determining the location of maximum dot product when iteratively comparing the signal averaged QRS complex from 50ms before to 50ms after the initial QRS detection of each beat. Bad beats, defined as QRST complexes with prematurity >5% of the pacing cycle length or a Pearson correlation coefficient <90% when compared to the average QRST complex, were replaced with the 128-beat window's average even or odd QRST complex as appropriate. Windows with >10% bad beats were excluded from analysis. After excluding the bad beats, the alignment was further refined by using the signal average QRS complex of only the good beats.

The pre-processed ECG was assessed for alternans in each 128-beat window using the spectral method. A 128 x *n* matrix was constructed corresponding to the amplitude of each aligned point in the 128-beat series, where *n* represents the number of sampled time points in the interval of interest (i.e. QRS or JT interval). A fast Fourier transform was applied to the amplitude series to generate power spectra for each time point, which were then summed to

generate an aggregate power spectrum. The unadjusted alternans magnitude was defined as the spectral power at a frequency of 0.5 cycles/beat ($power_{0.5}$), while the spectral power of the noise band was defined as the power of the preceding frequencies from 0.44 to 0.49 cycles/beat ($power_{0.44\text{-}0.49}$). The alternans mean noise (S_{NB}), signal to noise ratio (k value) and magnitude (V_{alt}) were calculated as follows:

$$S_{NB} = \sqrt{mean(power_{0.44-0.49})}$$

$$k\ value = \frac{(power_{0.5} - mean(power_{0.44-0.49}))}{\sigma(power_{0.44-0.49})}$$

$$V_{alt} = \sqrt{power_{0.5} - {S_{NB}}^2}$$

Table S1. QRSA and TWA noise in patients with and without VA.

	All Patients* (N=93)	VA- (N=75)	VA+ (N=18)	*P*
QRSA S_{NB}, µV				
V1	3.2 (2.0-4.3)	3.2 (2.1-4.3)	3.4 (2.3-4.8)	0.78
V2	3.7 (2.9-5.4)	3.7 (2.8-6.2)	3.3 (2.9-5.2)	0.54
V3	3.6 (2.7-5.4)	3.6 (2.9-5.5)	3.3 (2.4-5.4)	0.44
V4	3.9 (2.7-5.9)	3.9 (2.8-6.2)	3.6 (2.4-5.0)	0.48
V5	3.1 (2.5-4.5)	3.3 (2.5-4.5)	2.9 (2.3-4.0)	0.28
V6	2.7 (2.0-3.8)	2.7 (2.1-3.9)	2.6 (1.7-3.6)	0.44
TWA S_{NB}, µV				
V1	2.5 (1.7-3.5)	2.6 (1.7-3.8)	2.5 (2.0-3.2)	0.81
V2	2.9 (2.2-3.9)	3.0 (2.1-4.1)	2.8 (2.5-3.6)	0.94
V3	3.0 (2.2-4.3)	3.1 (2.2-5.0)	2.7 (2.3-4.3)	0.78
V4	3.0 (2.1-4.8)	3.2 (2.1-5.0)	2.8 (1.9-4.2)	0.52
V5	2.8 (1.9-3.5)	3.0 (2.0-3.7)	2.3 (1.7-3.4)	0.29
V6	2.3 (1.6-3.1)	2.4 (1.8-3.3)	2.1 (1.6-3.0)	0.35

QRSA – QRS alternans; S_{NB} – alternans mean noise; TWA – T wave alternans; VA – ventricular tachyarrhythmia

*Patients with ≥12 months follow-up

Table S2. QRSA/TWA Category Study Classification (N=95).

	Ventricular Pacing Rate (bpm)			
	100 (n=86)	**110 (n=85)**	**120 (n=85)**	***P* ***
QRSA/TWA Category				0.003
QRSA-/TWA-, n (%)	60 (70)	54 (64)	40 (47)	**0.001**†
QRSA+/TWA-, n (%)	12 (14)	9 (11)	6 (7)	0.424
QRSA-/TWA+, n (%)	4 (5)	5 (6)	20 (24)	**0.001**†
QRSA+/TWA+, n (%)	10 (12)	17 (20)	19 (22)	0.077

QRSA – QRS alternans; TWA – T wave alternans

*McNemar Test 100 vs. 120 bpm

†Individual category statistical significance at Bonferroni corrected p-value <0.0125

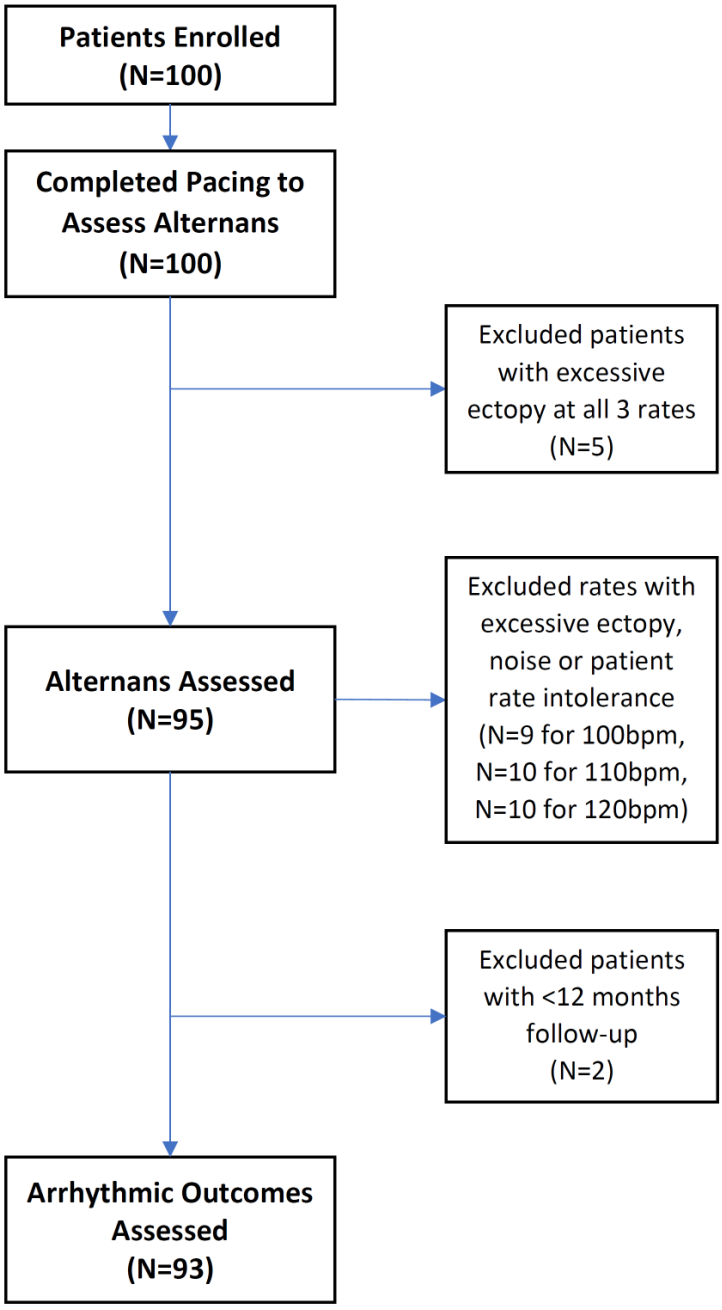
Table S3. Clinical characteristics of patients with and without QRSA.

	All Patients* (N=93)	QRSA- (N=51)	QRSA+ (N=42)	*P*
Age, yrs	62±11	63±11	62±9	0.787
Male sex, n (%)	80 (86)	42 (82)	38 (91)	0.370
LVEF, %	27±7	28±8	27±6	0.485
LVEF <35%, n (%)	78 (84)	42 (82)	36 (86)	0.780
Etiology of Cardiomyopathy				1.000
Ischemic, n (%)	59 (63)	32 (63)	27 (64)	
Non-ischemic dilated, n (%)	34 (37)	19 (37)	15 (36)	
NYHA functional class, n (%)				0.607
I	33 (36)	18 (35)	15 (36)	
II	41 (44)	24 (47)	17 (41)	
III	18 (19)	8 (16)	10 (24)	
IV	1 (1)	1 (2)	0 (0)	
Co-morbidities				
Hypertension, n (%)	47 (51)	28 (55)	19 (45)	0.408
Diabetes, n (%)	40 (43)	25 (49)	15 (36)	0.214
Prior revascularization, n (%)	48 (52)	27 (53)	21 (50)	0.836
Renal dysfunction†, n (%)	25 (27)	21 (41)	4 (10)	**0.001**
Medications				
Beta-blocker, n (%)	88 (95)	47 (92)	41 (98)	0.373
ACE-I/ARB, n (%)	84 (90)	46 (90)	38 (91)	1.000
Diuretic, n (%)	70 (75)	36 (71)	34 (81)	0.335
Class III anti-arrhythmic, n (%)	6 (7)	4 (8)	2 (5)	0.686
Calcium channel blockers, n (%)	2 (2)	2 (4)	0 (0)	0.499
Lipid-lowering agents, n (%)	72 (77)	39 (77)	33 (79)	1.000
Antiplatelet agents, n (%)	61 (66)	34 (67)	27 (64)	0.830
Traditional ECG Parameters				
Resting heart rate, bpm	68±11	69±12	67±10	0.307
QT interval, ms	426±40	422±38	432±42	0.239
QTc interval, ms	450±34	449±34	451±34	0.835
QRSd, ms†	118±27	113±24	124±30	**0.043**
QRSd ≥120ms, n (%)	41 (44)	21 (41)	20 (48)	0.675
LBBB, n(%)	17 (18)	8 (16)	9 (21)	0.592

ACE-I/ARB – angiotensin converting enzyme inhibitor / angiotensin II receptor blocker; LBBB – left bundle branch block; LVEF – left ventricular ejection fraction; NYHA – New York Heart Association; QRSd – QRS duration; VA – ventricular tachyarrhythmia

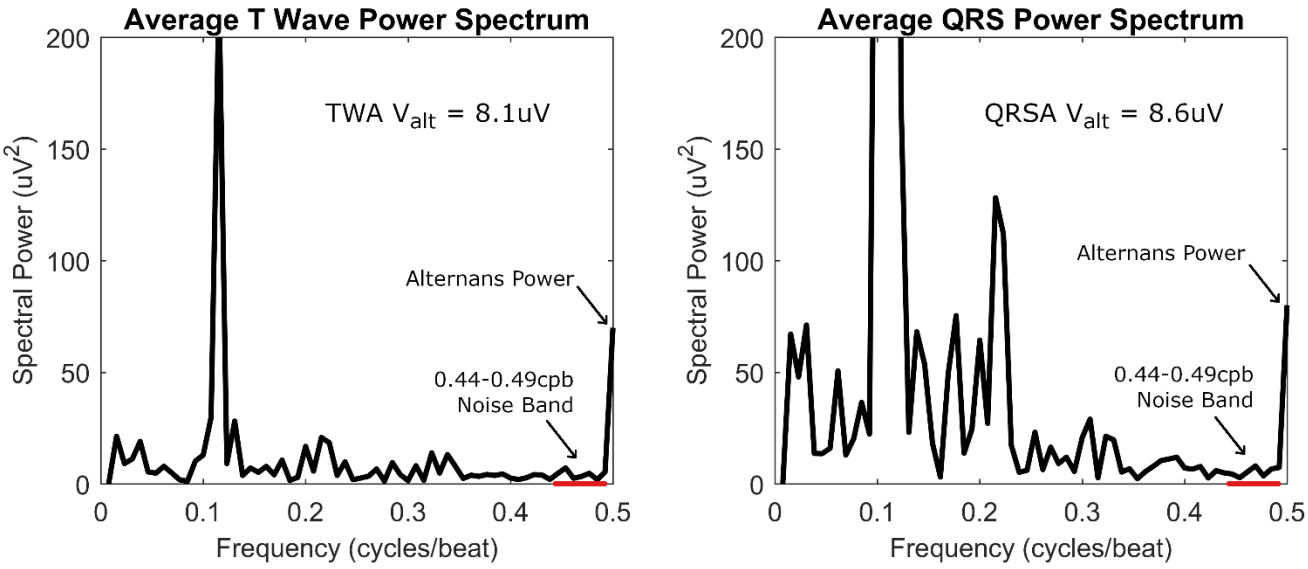
*Patients with ≥12 months follow-up; †eGFR<61mL/min/1.73m^2

Figure S1. Study Consort Diagram.



Consort diagram illustrating patient and pacing rate exclusions for alternans and arrhythmic outcomes assessments.

Figure S2. QRS and T Wave Power Spectra from a Patient with QRS and T Wave Alternans.



Plots illustrating the average T wave (left) and QRS (right) power spectra from a 128-beat segment of a representative patient with QRS and T wave alternans (same patient presented in Figure 4 of the manuscript). On both the T wave and QRS power spectra, a distinct alternans frequency peak is seen at 0.5 cycles/beat, while there is minimal spectral power in the frequencies of the noise band (0.44-0.49 cycle/beat) preceding it.